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Full Length Research Paper

Effects of curcuminoid on the liver function of patients with osteoarthritis

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Osteoarthritis is the most frequent joint disease worldwide. Patients with osteoarthritis mostly use non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac sodium for reducing pain. Diclofenac sodium frequently disturbs the liver function. Curcuminoid has an anti-inflammatory activity and some references state that curcuminoid protects the liver function. The purpose of this study was to compare the effects of curcuminoid from *Curcuma domestica* Val. *rhizome* extract and diclofenac sodium on the liver function of patients with osteoarthritis. A total of 80 patients with knee osteoarthritis were enrolled. Subjects were divided randomly into two groups; a group received 30 mg of curcuminoid from *C. domestica* Val. 3 times daily (curcuminoid group) and the other received 25 mg of diclofenac sodium 3 times daily (diclofenac group). Assessment of results includes serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) performed before and after 4 weeks of treatment. In the curcuminoid group, there was no significant decrease of AST serum level ($p < 0.15$) and ALT serum level ($p < 0.41$), whereas in the diclofenac group, there was no significant increase of AST serum level ($p=0.05$) and significant increase of ALT serum level ($p<0.01$). The increase of serum AST and ALT level in the diclofenac group were significantly different as compared to the decrease of the levels in the curcuminoid group. This means that diclofenac sodium disturbs liver function, while curcuminoid from *C. domestica* Val. rhizome extract improves the liver function of patients with osteoarthritis.

Key words: Curcuminoid, diclofenac sodium, liver function, osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the leading cause of musculo-skeletal disorders worldwide, and it became the second largest cause of physical disability after ischemic heart disease in patients over 50 years old. This disease causes a great loss of working hours and high treatment costs. Osteoarthritis was found worldwide with a pre-valence of less than 50 people per thousand populations in the population under 45 years old and increased in the sixth, seventh, and eighth decade. In the United States in

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2005, most of the population over the age of 65 years showed radiological signs of osteoarthritis (Dieppe, 2008). In the United States in 2000, the prevalence of OA in above 75 years old reached 800 persons per thousand population (Ratiner et al., 2001). This disease is associated with aging process. Osteoarthritis often influences the weight bearing joints, although sometimes it occurs generally. Traumatic histories of the joints increase the incidence of osteoarthritis (Hasan et al., 2006).

Curcuma domestica Val. is a native plant in Asia which is mainly used to reduce inflammation. Other than to reduce the inflammation, it is also used to maintain the freshness of the body, for seasoning, as in curries and food coloring, and to dye the skin in traditional ceremonies (Hasan et al., 2006). The rhizome of *C. domestica* Val. contains curcuminoid as much as 3 to 4% (consisting of curcumin, desmethoxycurcumin, and bisdesmethoxycurcumin), volatile oil as much as 2 to 5% (comprising sesquiterpene and phenylpropane derivates), arabinose, fructose, glucose, starch, tannin and minerals such as magnesium, manganese, iron, copper, calcium, sodium, potassium, zinc, cobalt, aluminum, and bismuth (Sudarsono et al., 1996). Curcumin has anti-inflammatory activity, prevents, and treats stomach ulcers, and also has anti-hepatotoxicity, cholagogic, and anti-tumor effect (Joe et al., 2004). Chainani (2003) through meta-analysis reported that in patients with rheumatoid arthritis, curcumin was able to reduce stiffness, joint swelling, and walking time. Turmeric extracts containing curcuminoid was able to prevent experimental rheumatoid arthritis (Funk et al., 2006).

Pain and loss of function are the main clinical features in osteoarthritis that lead to treatment, including non-pharmacological, pharmacological, and surgical approaches (Bijlsma and Berenbaum, 2011). Majority of patients with OA will require exercise, weight control, and pharmacotherapy. Analgesics, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), provide an effective option for pain management, but vary in regard to their safety and efficacy profiles. Selection of an appropriate agent should be based on an evaluation of pain severity, co-morbidities and concomitant medications, as well as efficacy and safety of the individual agents (Di Lorenzo, 2011). NSAIDs can be given if paracetamol treatment was considered to have failed to reduce the pain and improve joint function (Sharma, 2008).

In a previous study, by performing a clinical analysis and examination of blood and synovial fluid of patients with osteoarthritis for 2 years (1998 to 2000), the researcher found that the combination of 15 mg of *C. domestica* Val. rhizome extract and 100 mg essential oil of *Curcuma xanthorrhiza* Roxb. rhizome taken twice daily for 2 weeks time was comparable to the anti-inflam-matory drug piroxicam in lowering the malonyldialdehyde (MDA) level and leucocyte count of synovial fluid and improve the clinical symptoms of patients with knee osteoarthritis. Liver function was disturbed in using piroxicam, while it was improved in using the combination of curcuminoid and curcuma's essential oil (Kertia and Nurdjanah, 2004). Anti-inflammatory activities of cur-cumin were well explored and known. Curcumin was able to suppress the cyclooxygenase and lypoxygenase and it has an anti oxidative activity (Joe et al., 2004).

Alanine amino transferase (ALT) and aspartate amino transferase (AST) are two kinds of enzymes which are mostly used in detection of liver cell destruction (Thapa and Walia, 2007).

The aim of this study was to compare the effects of curcuminoid from *Curcuma domestica* Val. *rhizome* extract and diclofenac sodium on the liver function of patients with osteoarthritis.

MATERIALS AND METHODS

Extraction of the *C. domestica* Val. rhizome was conducted by sorting, then washing the rhizome which was then cut into pieces with a thickness of 1 to 2 mm and as dried with drying cupboard for 24 h at 40°C to obtain maximum water content of 10% v/w. The dried rhizome was then grilled to become powder. The powder was mixed with ethanol and then macerated for 24 h, then filtered with a Buchner funnel (with vacuum pressure). Collected filtrate was evaporated at 45°C in a vacuum condition. For the det ermination of curcuminoid, the curcumin standard solution was used with varying degrees of concentration. Extract obtained was diluted to 100 mg/ml and touched on silica gel GF 254 plates, and then eluted with a mobile phase system chloroform-methanol (97-3). Detection of spots was done by ultraviolet light 254 and 365 nm. The scanning was then performed by thin layer chromatography scanner. To calculate the concentration of curcumin, desmeto-xycurcumin, and bisdesmethoxycurcumin as components of curcuminoids, the standard used was pure curcumin. The linear regression method, $Y = a + bx$, where Y is the concentration of the standard, while a and b are constants of the standard; so, x (concentration of curcumin from curcuminoid) was found. The relative concentrations found were 52.93% curcumin, 21.63% desmetoxycurcumin, and 25.43% bisdesmethoxycurcumin. The extract was inserted into capsules with a dose of 30 mg curcuminoid per capsule. The other prepared capsules contain 25 mg of diclofenac sodium in each capsule.

Research subjects

Inclusion criteria: patients with knee OA aged more than 50 years, diagnosis was confirmed by the criteria of the American College of Rheumatology (ACR), agree to participate in this study with signed informed consent. Exclusion criteria: having arthritis other than osteoarthritis, having abnormalities of liver function, kidney or bone marrow function, having a history of gastritis, peptic ulceration or duodenal ulceration, hypersensitivity to turmeric or diclofenac sodium, using anticoagulant drugs or other NSAIDs.

Research site

This research was conducted in Rheumatology Clinic, Department of Internal Medicine, Faculty of Medicine, University of Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Table 1. Serum Levels of AST and ALT before and after treatment.

Variable	Diclofenac group			Curcuminoid group		
	Before (Mean ± SD)	After (Mean ± SD)	p (MD 95% CI (Lower, Upper)	Before (Mean ± SD)	After (Mean ± SD)	p (MD 95% CI (Lower, Upper)
AST (U/L)	23.80±10.59	25.15±8.35	0.05# (-3.45, 1.02)	21.59 ± 5.41	21.20 ± 4.29	0.15* (-0.79, 2.49)
ALT (U/L)	21.25±11.62	25.75±10.82	<0.01# (-7.49, -1.22)	20.56 ± 10.37	19.16 ± 8.19	0.41# (-1.41, 4.81)

p: level of significance; *Paired t-test; SD: Standard Deviation; #Wilcoxon Signed Ranks test; MD: Mean of difference; 95% CI: 95% Confidence interval.

Research design

Prospective randomized open end blinded evaluations (PROBE).

Research protocol

Study population was patients with knee OA who registered and are still able to be met in Dr. Sardjito General Hospital Yogyakarta. Random selection of the population was done by selecting patients who met the inclusion criteria and did not have any exclusion criteria. Wash-out was done in 1 week, followed by random assignment into treatment group and control group. Before starting the treatment, assessment of liver function (serum levels of AST and ALT) was evaluated. The treatment period was 4 weeks. The treatment group (curcuminoid group) was given 3 × 30 m g of curcuminoid from *C. domestica* Val. rhizome extract, while the control group (diclofenac group) was given 3 × 25 mg of diclofenac sodium. Evaluation of serum levels of AST and ALT was repeated after 4 weeks period of treatment. Data analysis was performed on the assessed variables before and after 4 weeks of treatment.

RESULTS AND DISCUSSION

A total of 80 patients with osteoarthritis of the knee were qualified and willing to participate in this study. Subjects were divided randomly into two groups, 39 subjects received 30 mg of curcuminoid from *C. domestica* Val. rhizome extract taken 3 times daily (curcuminoid group) and 41 subjects received 25 mg of diclofenac sodium taken 3 times daily (diclofenac group).

In the curcuminoid group, the number of subjects who participated in the study was 39 patients consisting of 15 men and 24 women. The mean age was 64.05 ± 8.83 years. The mean body mass index was 26.28 ± 3.62 kg/m^2. A total of 17 (43.6%) subjects had hypertension, 7 (17.9%) subjects had diabetes mellitus, 2 (5.1%) subjects suffer from heart failure, and 1 (2.6%) subject suffers from dyslipidemia. A total of five subjects were excluded with the reasons of one subject took piroxicam, one subject experienced abdominal colic due to urinary tract stones, one subject experienced hematuria due to urinary vesicles tumors, one subject stopped curcuminoid therapy as a request of the subject's family, and one subject had acute exacerbation of chronic obstructive pulmonary disease and stopped the curcuminoid therapy. The total number of subjects in the curcuminoid group who finished the study was 34 patients, consisting of 11 men and 23 women.

In the diclofenac group, the number of subjects who participated in the study was 41 patients consisting of 12 men and 29 women. The mean age was 64.56 ± 8.86 years. The mean body mass index was 26.44 ± 4.79 kg/m^2. A total of 14 (34.1%) subjects had hypertension, 6 (14.6%) subjects had diabetes mellitus, and 1 (2.4%) subject suffered dyslipidemia. A total of 2 subjects were excluded with the reasons: one subject experienced dyspepsia on the seventh day of therapy which did not improve with 10 mg omeprazole 1 tablet per day and one subject experienced diarrhea. The total number of subjects in the diclofenac group who finished the study was 39 patients, consisting of 11 men and 28 women.

Most subjects were women, which is consistent with the epidemiology of osteoarthritis which showed that the prevalence of osteoarthritis is higher in women than in men (Bijlsma and Berenbaum, 2011). When compared between the curcuminoid group and the diclofenac group, there was no significant difference in the frequency of sex.

The mean age of subjects was 64.05 ± 8.83 years in the curcuminoid group and 64.56 ± 8.86 years in the diclofenac group. This data indicates that osteoarthritis is more common in the elderly. This is consistent with epidemiological data that osteoarthritis is a degenerative disease. Osteoarthritis is a degenerative disease, so it is a chronic disease (Sharma, 2008). There was no signifi-cant difference in the mean age of both groups when comparing the curcuminoid group and the diclofenac group.

Co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, and heart failure were found in some subjects. Hypertension is the most frequent co-morbidity, followed by diabetes mellitus. Elderly people often have more than one disease in their body (Abdelhafiz, 2002); this is in accordance with the aforementioned data that there are several co-morbidities that occur in some patients with osteoarthritis. There was no significant diffe-rence in the percentage of co-morbidities between the curcuminoid group and the diclofenac group.

Table 1 present the average serum levels of AST and ALT in both groups before and after treatment. Serum levels of AST and ALT changed in both groups. In the group receiving curcuminoid, there was a decrease in the levels of AST and ALT; although, not statistically signifi-cant. In the group receiving diclofenac sodium, there was an increase of serum AST level, although, not signifi-cantly different, whereas the serum ALT level was significantly

Table 2. Average changes of serum AST and ALT level during treatment.

Variable	Diclofenac group (Mean ± SD)	Curcuminoid group (Mean ± SD)	p	MD 95% CI lower	MD 95% CI upper
AST (U/L)	-1.21 ± 6.99	0.85 ± 4.70	0.03#	-4.88	-0.75
ALT (U/L)	-4.35 ± 9.81	1.70 ± 8.91	<0.01#	-10.43	-1.68

p: level of significance; #Mann-Whitney U test; SD: Standard Deviation; MD: Mean of difference; 95% CI: 95% Confidence interval.

increased. The normal serum level of AST is less than 38 U/L and the normal serum ALT level is less than 41 U/L. Too many side effects can occur in long term use of NSAIDs especially in elderly people. These side effects for example are gastro intestinal tract bleeding and disturbance of liver and kidney function (Psaty and furberg, 2005).

The prevalence of hepatotoxicity caused by NSAIDs is about 1 to 8 cases every 100,000 use of NSAIDs. The hepatotoxicity mechanism of NSAIDs in general is due to hepatocellular toxicity and immunologic idiosyncrasy. Immunologic idiosyncrasy depends on the susceptibility of the patients to the drugs (O'Connor et al., 2003).

The average changes of serum AST and ALT level in both treatment groups are described in Table 2. In Table 2, it appears that the serum levels of AST and ALT increased in using the diclofenac sodium, while there was decrease in the levels using curcuminoid. Changes of AST and ALT serum levels were significantly different between both groups. The increase in serum levels of AST and ALT in the diclofenac group with the decrease in curcuminoid group indicated that treatment using diclofenac sodium causes disturbances of liver function, while treatment using curcuminoid tends to improve the liver function.

Liver is the biggest organ in the body with many functions. One of its important functions is drugs metabolism and enzyme secretion (Saladin, 2007). Amino transferase is a kind of enzyme which is mostly used in detection of liver cell destruction (Thapa and Walia, 2007). Chan et al. (2005) found that curcumin inhibits reactive oxygen species (ROS) formation and apoptosis in methylglyoxal-treated human hepatoma G2 cells. Medical researchers are needed to find out good evidences for development of herbs medicine (Braun and Cohen, 2005).

Conclusion

Increase in serum levels of AST and ALT in treatment using diclofenac sodium and the decrease in treatment using curcuminoid from *C. domestica* Val. rhizome extract indicated that treatment using diclofenac sodium causes disturbance of liver function, while treatment using curcuminoid tends to improve the liver function.

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